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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,044	01/14/2002	Mirella Ezban	5994.504-US	1706

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,044	EZBAN ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-23* is/are rejected.

7)☒ Claim(s) *18-20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-14-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

The Preliminary Amendment filed January 14, 2002 has been entered. Claims 1-16 have been cancelled. Therefore, Claims 17-22 are pending and have been considered in this Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17 and 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Taniguchi et al. (Cancer Res. (1998) 58: 4461-4467).

Taniguchi et al. teach that the expression of the urokinase receptor gene is upregulated in response to contacting factor VIIa to human pancreatic cancer cell lines that overexpress Tissue Factor (see abstract). Taniguchi et al. teach that the upregulation of the urokinase receptor gene can be reversed by coincubating the cells with factor VIIa and an anti-TF monoclonal antibody (Fig. 4).

Claims 17-18 and 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Pendurthi et al. (Proc. Natl. Acad. Sci. (1997) 94: 12598-12603).

Pendurthi et al. teach that contacting a fibroblast cell line with factor VIIa results in the upregulation of the gene encoding poly (A) polymerase (see abstract). Thus, Pendurthi et al. meets the limitations of Claims 17-18. Pendurthi et al. indicate that 10 nM of factor VIIa was contacted with the fibroblasts (see Figs. 1 and 2) in the method described therein. The method of Pendurthi et al. has the same steps as that of the presently claimed invention and uses the same cell type (fibroblasts) and same concentration of factor VIIa used in the present invention to cause the upregulation of Cyr61 (see example 12 of the present Specification). Thus, the method of Pendurthi et al., having the same steps and components as that of the presently claimed invention, would inherently have the same results (upregulation of Cyr61). Thus, Claims 21-23 are also anticipated by Pendurthi et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing expression of at least one gene in a cell line that constitutively expresses tissue factor, wherein the gene is selected from the group consisting of Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116 and P2U nucleotide receptor, does not reasonably provide enablement for a method of regulating the expression of at least one gene in a cell, comprising the step of

contacting said cell with a tissue factor agonist or antagonist, under conditions that result in a measurable change in said expression. More specifically, the specification does not provide enablement for 1) using the claimed method to *down regulate* the expression of a gene in a cell by contacting the cell with a tissue factor agonist or antagonist, 2) using an *antagonist or an agonist other than factor VIIa* to regulate expression of a gene; 3) regulating a gene in a cell other than a *cell line that constitutively expresses tissue factor* or 4) regulating the expression of any gene in any cell using antagonists or agonists of tissue factor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Practicing the invention commensurate in scope with the claims would require undue experimentation. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Breadth of the Claims:

Claim 17 encompasses a method of regulating the expression of any gene in any cell using any agonist or antagonist of tissue factor. Claim 18 and 19-20 are narrowed from claim 17 to define the agonist or antagonist used in the method but are

still open to the regulation of any gene in any cell. Claims 21-23 are narrowed from claim 17 to define the gene to be regulated but are still open to using any agonist or antagonist of tissue factor and using any cell.

Nature of the Invention:

The nature of the invention involves the identification of several genes, including Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116, and P2U nucleotide receptor, that are upregulated in tissue factor expressing cells that are contacted with factor VIIa, The nature of the invention requires the interaction of tissue factor with its agonist (factor VIIa) for the upregulation of the genes described.

Amount of Direction/Guidance Provided and Presence/Absence of Working Examples:

The present Specification provides guidance and working examples describing the upregulation of genes encoding Cyr61, CTFG, dopamine D2 receptor, EST Incyte PD 395116, the P2U nucleotide receptor, and the urokinase receptor gene. The present specification does not provide any guidance or working examples of regulating gene expression using any antagonists of factor VII or any agonists other than factor VIIa. There is also no guidance or working examples of regulating gene expression in vivo or using cells that do not express tissue factor.

State of the Prior Art/Relative Skill of those in the Art:

As evidenced by Taniguchi et al. and Pendurthi et al. described in the prior art rejections above, those of skill in the art were aware at the time of the present invention that factor VIIa could be used to upregulate gene expression. Taniguchi et al. teaches that contacting factor VIIa with human pancreatic cell lines that overexpress tissue

factor results in increased expression of the gene encoding the urokinase receptor. Pendurthi et al. teach that contacting a fibroblast cell line with factor VIIa results in the upregulation of the gene encoding poly(A) polymerase. However, upregulation of genes by factor VIIa appears to require tissue factor and proteolitically active factor VII (FVIIa) (see Camerer et al. (J. Biol. Chem. (1999) 274(45): 32225-32233 at p. 32231, Col. 2, paragraph 2). Camerer et al. show that while contact of FVIIa to cells expressing tissue factor upregulates egr-1 expression, active site inhibited FVIIa did not induce a response in egr-1 mRNA (see p. 32229, Col. 1, 3rd full paragraph). Pendurthi et al. (J. Biol. Chem. (2000) 275(19): 14632-14641) shows that factor VIIa catalytic activity is required for the induced expression of Cyr61 and that a factor VII modified with D-Phe-L-Phe-L-Arg chloromethyl ketone (active-site inactivated FVIIa) did not induce expression of Cyr61 (see Fig. 6 and p. 14633, Col. 1, "Proteins"). A search of the prior art indicates that the studies of factor VIIa induction of expression have only been in vitro and Camerer et al. indicates that it remains to be seen what the physiological impact of the in vitro observations will be since many physiological pathways seem to be affected by factor VIIa (see Camerer et al. (1999), p. 32232, last paragraph).

Predictability/Unpredictability:

Regulation of gene expression by contacting a protein to a cell involves many different proteins in a signal cascade and is thus very complex. The mechanism of how factor VIIa upregulates the genes is poorly understood. Thus, the predictability of what genes could be regulated, what tissue factor antagonists or agonists could be used to

regulate gene expression, and what cells other than cell lines that constituitively express tissue factor could be used is highly unpredictable.

Quantity of Experimentation:

For the reasons stated above, the quantity of experimentation to practice the claimed invention is considered undue. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the characterization of the mechanism by which factor VIIa, through its contact with tissue factor, upregulates gene expression. It is this additional characterization (that is required to predict with a reasonable expectation of success what tissue factor agonists or antagonists besides factor VIIa could be used in the method and what genes could be regulated by the method) that constitutes undue experimentation. Thus, the full scope of the claims is not considered enabled by the present Specification.

Claim Objections

Claims 18-20 are objected to for using the acronyms, FVII and FVIIa in Claims 18-19. The acronyms are inconsistent with the use of the full name in Claim 19. If acronyms are desired, the examiner suggests printing out the full name in the claim in which it first appears followed by the acronym in parenthesis. For example, Claim 18 could recite "factor VII (FVII), factor VIIa (FVIIa)" in line 2 and then the acronym could

be used in 20. Likewise, Claim 19 should be amended to have the full name of factor VII.

For the reasons stated above, Claim 22 is objected to for the acronym, CTFG. The claim should be amended to include the full name of the gene so that it is clear as to what gene is being referred.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
March 18, 2004

ROBERT A. WAX
PRIMARY EXAMINER